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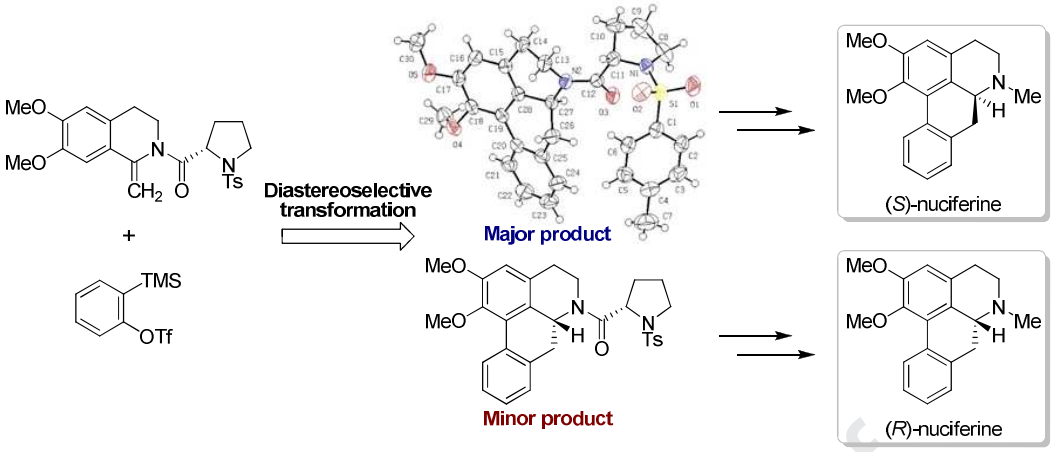
## Graphical Abstract



# Stereoselective total synthesis of (*S*)- and (*R*)-nuciferine using benzyne chemistry

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## Abstract

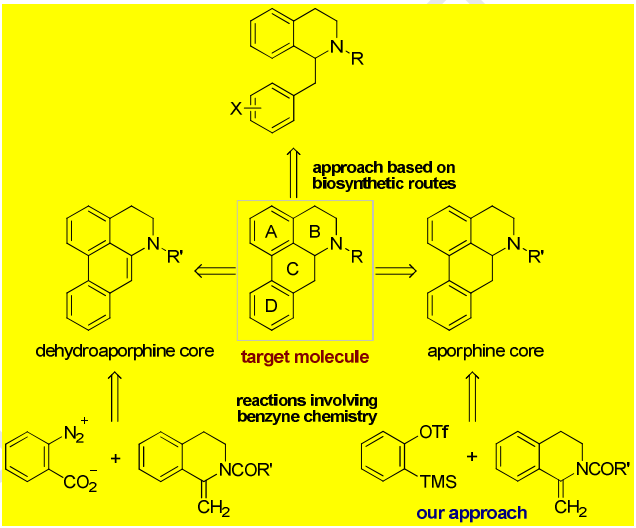
Total syntheses of (S)- and (R)-nuciferine were accomplished through approach involving diastereoselective reaction between a chiral dihydroisoquinoline enamide and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate promoted by CsF, affording a separable mixture of diastereoisomers, which provided (S)- and (R)-nuciferine via simple and efficient transformations.

**Keywords:** Stereoselective synthesis; Chiral auxiliary; Benzyne chemistry; DFT calculations; Aporphine alkaloids.

## 1. Introduction

Aporphine alkaloids are structurally characterized by a tetracyclic core containing a nitrogen atom and represent an important family of biosynthetic derivatives of isoquinoline alkaloids.[1] Aporphine compounds have important biological properties, for example, anticancer,[2] antiviral,[3] anti-inflammatory,[4] anti-HIV,[5] and leishmanicidal activities.[6] Among the aporphines, (±)-nuciferine may be featured due to its high affinity for the serotonin 5-$HT_{2A}$ receptor, which in therapeutic terms is related to several disorders, including schizophrenia, insomnia, and ischaemic heart disease.[7]

Because of the significant biological properties presented by aporphinoids, some synthetic approaches to produce aporphine cores have been developed.[8-15] The most widespread approach is based on biosynthetic routes and employs benzyltetrahydroisoquinoline intermediates for the C ring formation[8-14] through various transformations: 1) Pschorr reaction,[9] 2) phenolic couplings,[8,10] 3) nonphenolic couplings,[8,11] 4) photochemical reactions,[12] 5) acid-catalyzed reactions,[13] and 6) palladium-catalyzed reactions.[14] Complementarily, the approach that employs benzyne chemistry in the construction of the aporphine core has been extensively explored.[15-17] In this context, one can mention the reaction between 1-methyleneisoquinolines and arenodiazonium-2-carboxylates carried out under acidic conditions, which affords dehydroaporphines in moderate yields,[16] as well as the reaction between 1-methyleneisoquinolines and silylaryl triflates promoted by a source of fluoride ions, which allows the formation of aporphines in relatively high yields[17] (**Scheme 1**).



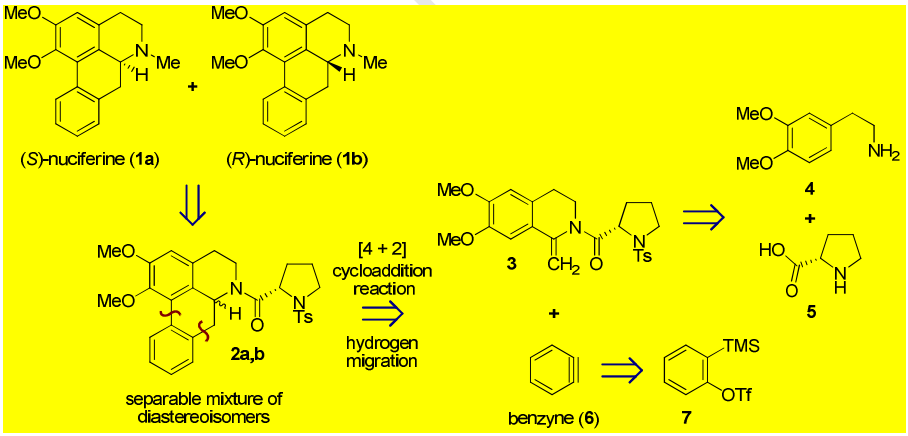

**Scheme 1.** Approaches to produce aporphine compounds.

In general, the reactions involving benzyltetrahydroisoquinoline intermediates[8-14] lead to aporphinoids in relatively low yields, employ transition metals, require high temperatures and strongly acidic conditions. Alternatively, the reaction between 1-methyleneisoquinolines and arenediazonium-2-carboxylates produces dehydroaporphines in moderate yields.[16] However, the use of anthranilic acid-derived aryne precursors has been discouraged for safety reasons.[15] Furthermore, a limited number of procedures is available for the reduction of dehydroaporphines to aporphines,[12d,12e] which is not a general transformation. Considering the reaction between 1-methyleneisoquinolines and silylaryl triflates, which has been explored in

our research group,[17] the introduction of chirality in the aporphine core may be considered a great challenge. Accordingly, in the present work we describe the total syntheses of (*S*)- and (*R*)-nuciferine through unprecedented approach involving diastereoselective reaction between chiral auxiliary-based isoquinoline compound and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate promoted by CsF, affording a separable mixture of diastereoisomers, which provided (*S*)- and (*R*)-nuciferine by simple and efficient transformations.

## 2. Results and Discussion

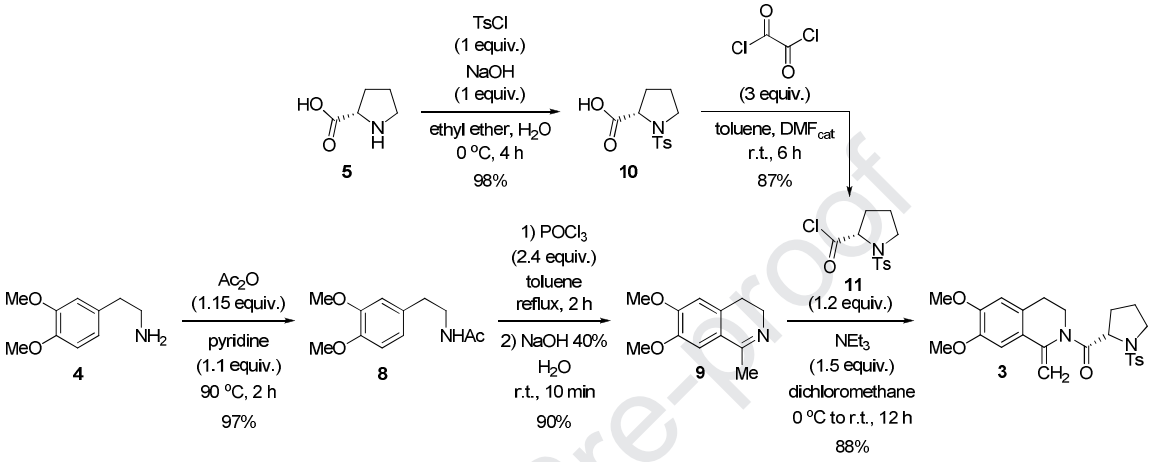
Our retrosynthetic analysis for (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**) is outlined in **Scheme 2**. Aporphine compounds **1a** and **1b** were prepared through the formation of a separable mixture of diastereoisomers **2a**,**b**, which was obtained by [4 + 2] cycloaddition reaction followed by hydrogen migration between chiral intermediate **3** and benzyne precursor **7**.[17] Chiral auxiliary-based intermediate **3** was produced from 3,4-dimethoxyphenethylamine (**4**) and L-proline (**5**).[17-20] Benzyne precursor **7** was obtained from a commercial source.




**Scheme 2.** Retrosynthetic analysis for (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**).

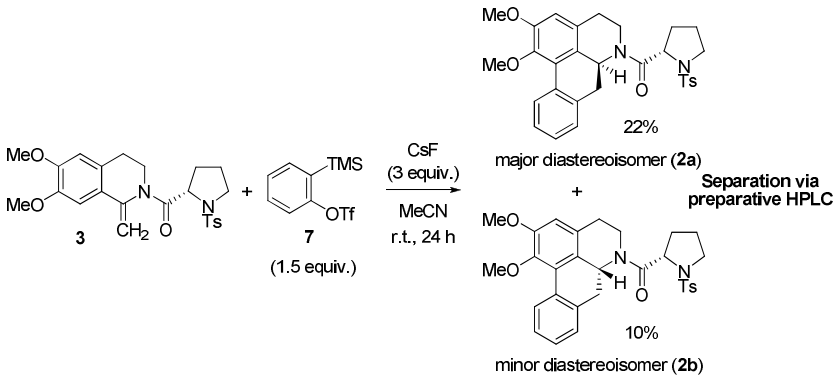
Total syntheses of (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**) were initiated through the production of chiral intermediate **3**.[17-20] Thus, 3,4-dimethoxyphenethylamine (**4**) was treated with acetic anhydride and pyridine leading to *N*-(3,4-dimethoxyphenethyl)acetamide (**8**) in 97% yield.[17,18] Amide **8** was converted by Bischler-Napieralski reaction to 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**9**) in 90% yield.[17,18] Concurrently, L-proline (**5**) was protected with *p*-toluenesulfonyl chloride in the presence of sodium hydroxide affording (*S*)-1-tosylpyrrolidine-2-carboxylic acid (**10**) in 98% yield.[19] Protected amino acid **10** was allowed to react with

oxalyl chloride using *N*,*N*-dimethylformamide in catalytic amount to give (*S*)-1-tosylpyrrolidine-2-carbonyl chloride (**11**) in 87% yield.[20] Subsequently, we carried out the reaction between dihydroisoquinoline **9** and chiral acid chloride **11** in the presence of triethylamine and obtained chiral isoquinoline compound **3** in 88% isolated yield[17] (**Scheme 3**). The conditions for the preparation of compound **3** were optimized after an extensive series of experiments.




**Scheme 3.** Synthesis of intermediate **3**.

Afterwards, allowing the key reaction between chiral isoquinoline compound **3** and benzyne precursor **7** in the presence of CsF using acetonitrile as solvent,[17] we observed the formation of a mixture containing diastereoisomers **2a** and **2b** in the proportion of 2.3:1, respectively, according to liquid chromatography-high resolution mass spectrometry (LC-HRMS) analysis (**Scheme 4**). Derivatives of diastereoisomers **2a** and **2b** containing pyrrolidine rings protected with Boc or Cbz groups could not be obtained by transformations outlined in **Schemes 3** and **4**.




**Scheme 4.** Preparation of diastereoisomers **2a** and **2b**.

Compounds **2a** and **2b** formed a mixture inseparable by column chromatography or preparative thin-layer chromatography. Thus, the mixture containing compounds **2a** and **2b** was isolated by column chromatography to remove the remaining starting materials and unidentified by-products. Then, diastereoisomers **2a** and **2b** were separated by preparative high-performance liquid chromatography (HPLC) in yields of 22% and 10%, respectively (**Scheme 4**).

The structure of the major diastereoisomer **2a** was unequivocally confirmed by X-ray analysis (**Figure 1**) (see Supporting Information).

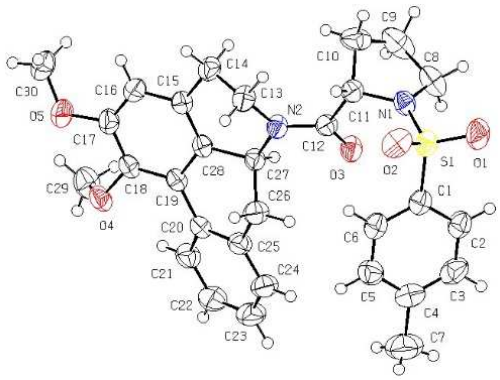



**Figure 1.** ORTEP representation of compound **2a**.

DFT calculations were carried out to evaluate the stereochemical pathway that led to the formation of diastereoisomers **2a** and **2b** in the proportion of 2.3:1, respectively (**Scheme 4**). According to the calculations in acetonitrile, the reaction between compound **3** and benzyne (**6**), presumably generated in the reaction medium, provided intermediates **A** and **A'** through a concerted [4 + 2] cycloaddition reaction, involving transition states with a considerable difference in energy, namely, **TS (A)** with 7.91 kcal $mol^{-1}$ and **TS (A')** with 12.37 kcal $mol^{-1}$. Then, intermediates **A** and **A'** were converted to diastereoisomers **2a** and **2b** by a hydrogen migration via **TS (2a)** and **TS (2b)** transition states with energies of 10.42 kcal $mol^{-1}$ and 11.48 kcal $mol^{-1}$, respectively. The total process is spontaneous by -38.41 kcal $mol^{-1}$ considering compound **2a** and by -21.48 kcal $mol^{-1}$ taking into account compound **2b**. Optimized geometries in Cartesian coordinates for all species can be found in the Supporting Information. The obtained results have illustrated that the concerted [4 + 2] cycloaddition reaction may be considered the determining step for the diastereoselectivity of the transformation (**Figure 2**).

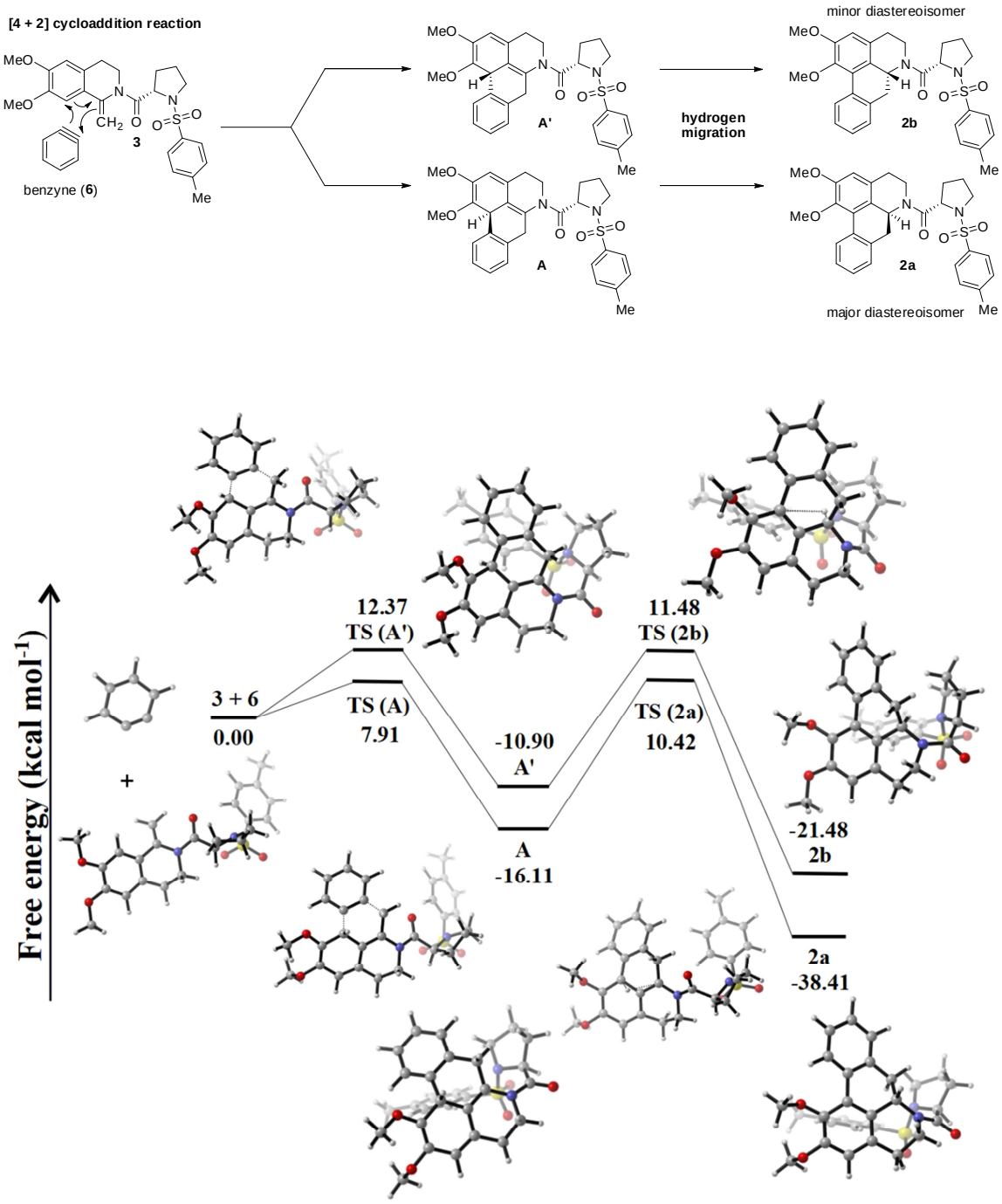
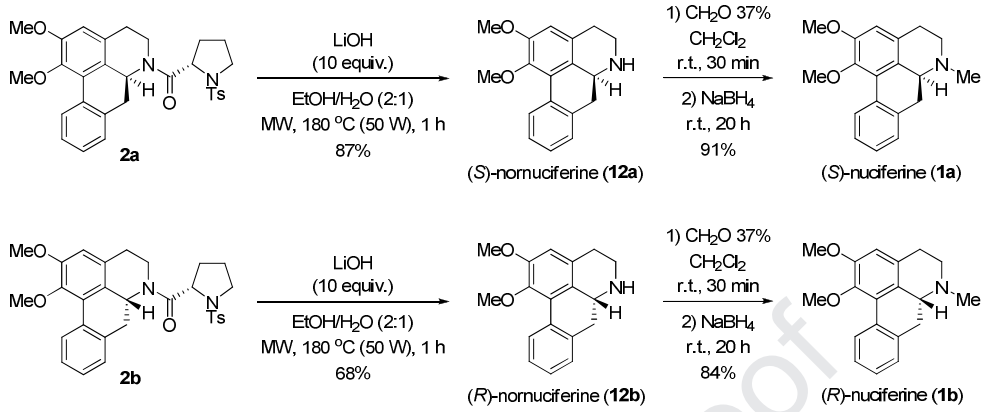



**Figure 2.** Proposed stereochemical pathway evaluated by DFT calculations for diastereoisomers **2a** and **2b**.

Afterwards, diastereoisomers **2a** and **2b** were subjected to basic hydrolysis reaction with lithium hydroxide in a mixture of ethanol/water (2:1) under microwave heating,[17a,c] affording (*S*)-nornuciferine (**12a**) and (*R*)-nornuciferine (**12b**) in yields of 87% and 68%, respectively. No attempt was made to recover the chiral auxiliary. Then, we submitted (*S*)-nornuciferine (**12a**) and (*R*)-nornuciferine (**12b**) to *N*-methylation reaction with formaldehyde followed by sodium borohydride reduction[17] leading to (*S*)-

nuciferine (**1a**) and (*R*)-nuciferine (**1b**) in yields of 91% and 84%, respectively (**Scheme 5**). The total syntheses of (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**) were accomplished through 6 reaction steps with overall yields of 13% and 4%, respectively.




**Scheme 5.** Transformations to achieve (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**).

The structures of compounds **8**, **9**, **10**, and **11** were assigned according to their LRMS, IR, $^{1}$H, and $^{13}$C NMR spectra. HRMS, IR, $^{1}$H, and $^{13}$C spectra were obtained to confirm the structure of compound **3**. The structures of compounds **2a** and **2b** were assigned according to their HRMS, IR, $^{1}$H, $^{13}$C, and HSQC NMR spectra. Compounds **12a** and **1a** had their structures assigned by LRMS, IR, $^{1}$H, and $^{13}$C NMR spectra. Compound **12b** and **1b** had their structures confirmed by LRMS and $^{1}$H NMR spectra. Solid substances (**8**, **9**, **11**, **3**, **2a**, **2b**, **1a** and **1b**) had their melting point values determined and chiral compounds (**10**, **11**, **3**, **2a**, **2b**, **12a**, **12b**, **1a**, and **1b**) had their optical rotation measured. The optical rotations of compounds **1a** and **1b** matched those reported for the corresponding natural products (*S*)-nuciferine[21] and (*R*)-nuciferine.[14c] Chiral HPLC analyses were performed to confirm the high enantiomeric purity of compound **1a**.

## 3. Conclusions

In summary, the total syntheses of (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**) were accomplished through unprecedented approach involving diastereoselective reaction between chiral auxiliary-based isoquinoline compound **3** and benzyne precursor **7** promoted by CsF, affording a separable mixture of diastereoisomers **2a** and **2b**, which provided (*S*)-nuciferine (**1a**) and (*R*)-nuciferine (**1b**), respectively, via simple and efficient transformations. The stereochemical pathway for the reaction between compound **3** and benzyne (**6**) was outlined by DFT calculations in acetonitrile. The

chemistry disclosed in this work represents an advance for the stereoselective synthesis of aporphine alkaloids involving benzyne chemistry.

## 4. Experimental

### *4.1. General information*

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a spectrometer operating at 300 MHz and 75 MHz, respectively. $^{1}H$ NMR spectra were taken in deuterated solvents and the chemical shifts are given in ppm with respect to TMS used as internal standard, except when indicated in the spectrum. $^{13}C$ NMR spectra were taken in deuterated solvents and the chemical shifts are given in ppm with respect to the deuterated solvent used as reference. HSQC spectra were registered on a 300 MHz NMR spectrometer. IR spectra were obtained using attenuated total reflectance (ATR) or KBr pellets in the 4000-400 $cm^{-1}$ region. Mass spectra were carried out employing a gas chromatograph coupled to a quadrupole mass spectrometer using electron ionization at 70 eV. High-resolution mass spectra were obtained using a hybrid quadrupole/time-of-flight (Q-Tof) mass spectrometer. Melting point values are uncorrected. Specific optical rotation analyses were obtained with a digital polarimeter using a short cuvette (0.5 dm) and the D-line of the sodium lamp (589 nm) at 21-25 $^{o}C$. Diastereoisomers **2a** and **2b** were quantified in mixture via LC-PDA-HRMS analysis (mobile phases: (A) MeOH and (B) 10 mM aqueous solution of ammonium formate (70:30); column: Restek Ultra PFPP 100 x 2.1 mm, 3 µm; flow: 0.1 mL/min; column temperature: r.t.). Diastereoisomers **2a** and **2b** were separated via preparative HPLC (mobile phase: (A) $H_2O$ + 20 mM ammonium formate and (B) MeOH/ACN 85:15 (33:67); column: Phenomenex Luna Phenyl-Hexyl 150 x 21.20 mm, 5 µm; flow: 15 mL/min; column temperature: r.t.). Chiral HPLC analyses for (±)-nuciferine and (*S*)-nuciferine (**1a**) are shown in **Figures 2S**, **3S**, and **4S** available in the Supporting Information. (±)-Nuciferine was obtained according to the literature.[17b] Column chromatography separations were carried out using 70-230 mesh silica gel. Preparative TLC separations were carried out using silica gel matrix with inorganic binder and fluorescent indicator. Commercially obtained reagents were employed without further purification. High purity CsF (99.99%) was used in the experiments. Solvents were treated when necessary according to the literature.[22] MeCN was distilled from $CaH_2$ under anhydrous conditions prior to use.[22] *n*-BuLi was titrated against *s*-BuOH using 1,10-phenanthroline as indicator under $N_2$ atmosphere.[23] LDA was generated following the typical procedure before use.[24] Suitable single crystals for

X-ray diffraction were grown by slow evaporation of a solution 1:1 (v/v) methanol/dichloromethane containing **2a**. The data were collected on a BRUKER KAPPA APEX II Duo diffractometer using graphite-monochromated CuKa radiation (λ = 1.54178 Å) at 296 K. Standard procedures were used for data reduction and multi-scan absorption correction was applied. The structure was solved using direct methods with SHELXS-97[25] and refined with anisotropic displacement factors for all non-hydrogen atoms and with the hydrogen atoms being positioned using the riding model of SHELXL-2014.[26] Additional crystal data and refinement details for **2a** are presented in **Table 1S** and bond lengths [Å] and angles [°] are shown in **Table 2S** that are available in the Supporting Information. Crystallographic information on the structure determination has been deposited at Cambridge Crystallographic Data Center. CCDCD 1993331 data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: de-posit@ccdc.cam.ac.uk. All quantum mechanical calculations were carried out using Gaussian 16 (Revision B.01)[27] employing the Becke's three-parameter hybrid exchange functional combined with Lee-Yang-Parr correlation functional (B3LYP)[28,29] at the 6-31+G(d,p) level. The geometry optimization was computed using Berny's optimization algorithm and the calculations of harmonic vibrational frequencies were also performed for all the stationary points. For each optimized ground state, the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency. The energies reported in this work include the zero-point vibrational energy corrections (ZPVE) and are not scaled. All transition structures (TSs) were obtained using the QST2/QST3 as implemented in Gaussian. Visual inspection of the corresponding normal mode was used to confirm that the correct transition state had been found. The Self-Consistent Isodensity Polarizable Continuum Model (SCIPCM)[30] model approach was used for the single point calculations in acetonitrile. The 3D structural representations were generated using CYLview software.[31]

*4.2. General procedures*

*N-(3,4-dimethoxyphenethyl)acetamide (**8**)*[17,18]

To a round-bottomed flask equipped with a reflux condenser were added 3,4-dimethoxyphenethylamine (**4**) (1.81 g, 10 mmol, 1.70 mL), acetic anhydride (1.17 g,

11.5 mmol, 1.10 mL), and dry pyridine (870 mg, 11 mmol, 0.90 mL). The mixture was maintained under stirring and anhydrous conditions at 90 $^{o}$C for 2 hours. Afterwards, the reaction mixture was poured into a beaker containing crushed ice (40 g), and the resulting mixture was stirred with a glass rod for 5 min. Then, the mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with 10% (w/v) aqueous solution of $NaHCO_3$ (100 mL), saturated aqueous solution of $CuSO_4$ (100 mL), and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording desired product **8**. Yield: 2.17 g (97%); off-white solid; m.p. 99-100 °C (m.p. lit.[32] 100-102 °C); $R_f$ = 0.81 (eluent: methanol); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 6.82-6.79 (m, 1H), 6.74-6.72 (m, 2H), 5.96 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.48 (q, *J* = 6.7 Hz, 2H), 2.76 (t, *J* = 7.1 Hz, 2H), 1.94 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 170.0, 148.8, 147.4, 131.2, 120.4, 111.7, 111.2, 55.7, 55.6, 40.6, 35.0, 23.0; IR (KBr, $cm^{-1}$) 3251.9, 3080.3, 2972.3, 2927.9, 1663.7, 1608.6, 1566.2, 1516.0, 1417.6, 1377.1, 1261, 4, 1035.7; GC/MS (*m/z*, %): 223 (7.3), 180 (0.3), 164 (100.0), 151 (41.6), 121 (4.1), 108 (3.4), 107 (7.9). Characterization data are in accordance with the literature.[17b,32]

*6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**9**)*[17,18]

To a round-bottomed flask equipped with a reflux condenser were added *N*-(3,4-dimethoxyphenethyl) acetamide (**8**) (0.89 g, 4 mmol) and toluene (4.50 mL). The mixture was heated to 40 °C under stirring and $N_2$ atmosphere. Then, $POCl_3$ (1.47 g, 9.6 mmol, 0.90 mL) was added dropwise using syringe and needle. The reaction was maintained under reflux for 2 hours and cooled using an ice bath for 4 h. The solvent was evaporated under reduced pressure, affording an intermediate salt (m.p. 146-149 ºC (m.p. lit.[18b] 148-152 ºC)). After that, the intermediate salt was dissolved in water (10 mL) and a 40% (w/v) aqueous solution of NaOH (10 mL) was added to the mixture, which was maintained under stirring for 10 minutes. The reaction was extracted with $CHCl_3$ (3 x 20 mL). The organic phase was washed with distilled water (10 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording desired product **9**. Yield: 0.74 g (90%); brownish solid; m.p. 102-103 °C (m.p. lit.[18b] 105-107 °C); $R_f$ = 0.38 (eluent: methanol); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 6.99 (s, 1H), 6.69 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3,63 (tq, *J* = 7.6 Hz, 1.4 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 1.4 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 163.6, 150.8, 147.4, 131.0, 122.4, 110.1, 108.9, 56.1, 55.9, 46.9, 25.7, 23.3; IR (KBr,

$cm^{-1}$) 2993.5, 2962.6, 2922.1, 1602.8, 1514.1, 1408.4, 1350.1, 1213.2, 1060.8; GC/MS (*m/z*, %): 205 (100.0), 190 (57.9), 174 (21.5), 160 (21.4), 147 (12.8), 132 (4.3). Characterization data are in accordance with the literature.[17b,32]

*(S)-1-tosylpyrrolidine-2-carboxylic acid (**10**)*[19]

To a round-bottomed flask containing L-proline (**9**) (5.76 g, 50 mmol) was added a 2 M aqueous solution of NaOH (50 mL, 100 mmol) under stirring at 0 $^{o}$C. The mixture was warmed to room temperature and a solution of *p*-toluenesulfonyl chloride (9.53 g, 50 mmol) in diethyl ether (10 mL) was added dropwise using syringe and needle. The reaction was maintained under stirring at 0 °C for 4 hours. Afterwards, at room temperature, the aqueous solution was separated from the organic phase and acidified to pH 2 with concentrated HCl. The mixture was extracted with ethyl acetate (3 x 15 mL). The organic phase was washed with 10% aqueous solution of NaCl (20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure, affording desired product **10**. Yield: 13.18 g (98%); yellowish oil; $R_f$ = 0.56 (eluent: EtOAc); $[\alpha]_D^{23}$ = -89.8° (*c* = 3.05 MeOH) ($[\alpha]_D^{26}$ lit.[19] = -83.9° (*c* = 3.05 MeOH)); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 9.32 (s, 1H), 7.76-7.73 (m, 2H), 7.33-7.31 (m, 2H), 4.26 (dd, *J* = 7.9 Hz, 3.8 Hz, 1H), 3.53-3.46 (m, 1H), 3.29-3.21 (m, 1H), 2.42 (s, 3H), 2.12-1.90 (m, 3H), 1.78-1.69 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 176.7, 144.0, 134.3, 129.8, 127.5, 60.3, 48.7, 30.6, 24.6, 21.5; IR (KBr, $cm^{-1}$) 3570.2, 3485.3, 3089.9, 2978.0, 2552.8, 1764.8, 1494.8, 1344.3, 1093.6; GC/MS (*m/z*, %): 224 (82.3), 155 (63.6), 91 (100.0), 70 (35.5). Characterization data are in accordance with the literature.[19]

*(S)-1-tosylpyrrolidine-2-carbonyl chloride (**11**)*[20]

To a round-bottomed flask containing (*S*)-1-tosylpyrrolidine-2-carboxylic acid (**10**) (1.21 g, 4.5 mmol) and toluene (35 mL) were added oxalyl chloride (1.07 mL 12.3 mmol) dropwise using syringe and needle and dimethylformamide (DMF) (5 µL). The mixture was maintained under stirring at room temperature for 6 hours. Afterwards, the reaction was evaporated under reduced pressure. To the round-bottomed flask containing the material obtained was added hot hexane (100 mL) and the mixture was capped and maintained in the refrigerator for 12 hours. After vacuum filtration, desired product **11** was obtained. The crystallization process was performed 6 times. Yield: 1.12 g (87%); off-white solid; m.p. 57-58 °C (m.p. lit.[20] = 57-59 °C); $R_f$ = 0.72 (eluent:

EtOAc); $[\alpha]_D^{23}$ = -69.1° (*c* = 2.1 MeOH) ($[\alpha]_D^{20}$ lit.[20] = -64.1° (*c* = 2.1 benzene); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 7.76-7.74 (m, 2H), 7.35-7.32 (m, 2H), 4.62 (t, *J* = 6.8 Hz, 1H), 3.53-3.46 (m, 1H), 3.40-3.34 (m, 1H), 2.44 (s, 3H), 2.23-2.16 (m, 2H), 2.02-1.93 (m, 1H), 1.87-1.81 (m, 1H); $^{13}$C NMR (75 MHz, CDCl 3, ppm): δ 174.0, 144.2, 134.9, 129.9, 127.5, 68.7, 48.6, 30.6, 24.3, 21.6; IR (KBr, $cm^{-1}$) 2951.0, 2891.3, 1811.1, 1597.0, 1344.3, 1155.3, 1010.7, 943.1, 663.5; GC/MS (*m/z*, %): 224 (100.0), 155 (56.9), 91 (65.0). Characterization data are in accordance with the literature.[20]

*(S)-(6,7-dimethoxy-1-methylene-3,4-dihydroisoquinoline-2(1H)-yl)(1-tosylpyrrolidin-2-yl)methanone (**3**)*[17]

To a round-bottomed flask were added 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**9**) (205 mg, 1 mmol), (*S*)-1-tosylpyrrolidine-2-carbonyl chloride (**11**) (350 mg, 1.2 mmol), dichloromethane (10 mL), and dry triethylamine (0.21 mL, 1.5 mmol). The round-bottomed flask was capped with a rubber septum. Then, the reaction was cooled to 0 °C and maintained under stirring for 1 hour. Afterwards, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (1.25:0.75) as eluent, affording desired product **3**. Yield: 0.40 g (88%); yellowish solid; m.p. 146-148 °C; $R_f$ = 0.52 (eluent: ethyl acetate/hexane (1.25:0.75); $[\alpha]_D^{21}$ = -148.5° (*c* = 0.1 MeOH); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 7.47-7.44 (m, 2H), 7.11-7.08 (m, 2H), 7.01 (s, 1H) 6.53 (s, 1H), 5.50 (s, 1H), 4.93 (s, 1H), 4.89 (t, *J* = 7.8 Hz, 1H), 4.19-4.12 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.36-3.58 (m, 1H), 3.51-3.44 (m, 1H), 3.35-3.27 (m, 1H), 2.92-2.82 (m, 1H), 2.68-2.60 (m, 1H), 2.30 (s, 3H), 2.02-1.80 (m, 3H), 1.67-1.61 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 200.2, 171.2, 150.0, 147.7, 143.1, 143.0, 135.6, 129.4, 127.5, 123.3, 111.4, 106.6, 104.4, 62.6, 57.4, 56.1, 55.9, 49.0, 31.9, 28.4, 24.9, 21.5; IR (KBr, $cm^{-1}$) 3431.4, 3132.4, 2968.4, 2939.5, 2883.6, 1668.4, 1606.7, 1512.1, 1408.4, 1338.6, 1271.0, 1157.2, 1074.3; HRMS calculated for $[C_{24}H_{29}N_2O_5S]^+$ 457.1792, found $[C_{24}H_{29}N_2O_5S]^+$ 457.1799.

*(S)-1,2-Dimethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinolin-6(5H)-yl)((S)-1-tosylpyrrolidin-2-yl)methanone (**2a**) and (R)-1,2-dimethoxy-6a,7-dihydro-4H-dibenzo[de,g] quinolin-6(5H)-yl)((S)-1-tosylpyrrolidin-2-yl) methanone (**2b**)*[17]

To a vial (20 mL) were added chiral intermediate **3** (228 mg, 0.5 mmol), silylphenyl triflate **6** (223 mg, 0.75 mmol), acetonitrile (5 mL), and CsF (228 mg, 1.5 mmol). The

vial was sealed using a cap, and and the mixture was maintained under stirring at room temperature for 24 hours. Afterwards, brine (20 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was pre-purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (1.25:0.75) as eluent, affording a mixture containing desired diastereoisomers **2a** and **2b** ($R_f$ = 0.62) in the ratio of 2.3:1, respectively, according to LC-HRMS analysis. Diastereoisomers **2a** and **2b** were separated via preparative HPLC. Diastereoisomer **2a**. Yield: 59.6 mg (22%); off-white solid; m.p. 99-101 °C; $R_f$ = 0.63 (eluent: ethyl acetate); $[\alpha]_D^{23}$ = +60.8º (*c* = 0.07 MeOH); $^1$H NMR (300 MHz, $CDCl_3$, ppm) (for a mixture of rotamers in a ratio of 2:1): δ 8.49 (d, *J* = 7.4 Hz, 1H), 8.40 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 4H), 7.48 (d, *J* = 7.0 Hz, 2H), 7.41-7.24 (m, 13H), 7, 08 (d, *J* = 7.0 Hz, 2H), 6.70 (s, 1H), 6.66 (s, 2H), 4.97-4.46 (m, 6H), 4.54 (s, 1H), 4.21 (d, *J* = 12.6 Hz, 2H), 3.89 (s, 9H), 3.66 (s, 9H), 3.50-3.47 (m, 6H), 3.34 (t, *J* = 12.1 Hz, 2H), 3.16 (t, *J* = 14.2 Hz, 1H), 2.93-2.82 (m, 4H), 2.76-2.59 (m, 7H), 2.45 (s, 6H), 2.34 (s, 3H), 2.11-2.03 (m, 7H), 1.99-1.93 (m, 3H), 1.82-1.74 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) (for a mixture of rotamers): δ 171.8, 169.7, 152.2, 152.0, 145.8, 145.6, 143.3, 136.6, 136.1, 135.6, 135.5, 135.1, 135.0, 131.7, 131.6, 131.4, 131.3, 130.1, 129.5, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 127.2, 126.8, 126.1, 125.3, 125.2, 111.6, 111.1, 59.9, 58.7, 57.1, 57.0, 55.9, 52.9, 52.9, 51.2, 48.9, 48.9, 48.3, 41.0, 37.9, 37.3, 33.7, 32.0, 30.6, 29.6, 25.1, 24.6, 21.5, 21.4; IR (KBr, $cm^{-1}$) 2916.4, 2835.4, 1639.4, 1597.6, 1492.9, 1421.5, 1334.7, 1109.1, 1159.2, 1039.6, 937.4, 663.5; HRMS calculated for $[C_{30}H_{33}N_2O_5S]^+$ 533.2105, found $[C_{30}H_{33}N_2O_5S]^+$ 533.2107. Diastereoisomer **2b**. Yield: 26.1 mg (10%); off-white solid; m.p. 121-123 °C; $R_f$ = 0.65 (eluent: ethyl acetate); $[\alpha]_D^{25}$ = -231.3º (*c* = 0.07 MeOH); $^1$H NMR (300 MHz, CDCl 3, ppm) (for a mixture of rotamers in a ratio of 1:1): δ 8.49 (d, *J* = 7.0 Hz, 1H), 8.44 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.47-7.29 (m, 6H), 7.24-7.19 (m, 4H), 6.70 (s, 1H), 6.69 (s, 1H), 5.03-4.87 (m, 2H), 4.74 (dd, *J* = 8.5 Hz, 3.3 Hz, 1H), 4.48 (dd, *J* = 13.8 Hz, 3.1 Hz, 1H), 4.29-4.17 (m, 2H), 3.90 (s, 6H), 3.67 (s, 6H), 3.54-3.47 (m, 2H), 3.41-3.06 (m, 7H), 2.95 (dd, *J* = 13.5 Hz, 3.9 Hz, 1H), 2.81-2.70 (m, 4H), 2.41 (s, 3H), 2.33 (s, 3H), 2.13-2.10 (m, 2H), 2.06-1.99 (m, 3H), 1.94-1.87 (m, 2H), 1.72-1.68 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm) (for a mixture of rotamers): δ 171.0, 169.8, 152.4, 152.0, 145.7, 143.4, 143.3, 136.5, 136.4, 136.1, 136.0, 131.6, 131.5, 126.9, 126.9, 126.1, 126.0, 125.1, 129.9,

129.9, 129.5, 129.4, 129.2, 129.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 111.5, 111.2, 60.0, 58.7, 58.6, 55.9, 52.8, 50.9, 48.5, 48.0, 41.0, 36.8, 36.4, 33.7, 31.9, 31.3, 30.6, 29.9, 29.6, 29.3, 24.8, 24.7, 21.5, 21.4; IR (KBr, $cm^{-1}$) 2924.1, 1728.2, 1649.4, 1595.1, 1448.5, 1443.5, 1338.2, 1155.3, 1107.1, 1031.9, 663.5, 590.2; HRMS calculated for $[C_{30}H_{33}N_2O_5S]^+$ 533.2105, found $[C_{30}H_{33}N_2O_5S]^+$ 533.2114.

*(S)-nornuciferine (**12a**)*[17]

To a microwave tube (10 mL) were added diastereoisomer **2a** (41.3 mg, 0.078 mmol), ethanol/water (2:1) (6 mL), and lithium hydroxide (32.8 mg, 0.78 mmol). The tube was sealed using a cap and the mixture was stirred under microwave heating at 180 °C (50 W) for 60 minutes. Then, the reaction was cooled to room temperature and distilled water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 15 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent, affording (*S*)-nornuciferine (**12a**). Yield: 19.0 mg (87%); yellowish oil; $R_f$ = 0.26 (eluent: methanol); $[\alpha]_D^{25}$ = +131.9º (*c* = 0.19 EtOH) ($[\alpha]_D^{22}$ lit[33] = +140º (*c* = 0.18 EtOH)); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.19-7.11 (m, 3H), 6.54 (s, 1H), 3.77 (s, 3H), 3.70 (dd, *J* = 13.4 Hz, 4.5 Hz, 1H), 3.57 (s, 3H), 3.26-3.23 (m, 1H) 2.95-2.83 (m, 2H), 2.76-2.56 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 152.0, 145.1, 136.1, 132.1, 128.8, 128.7, 128.3, 127.7, 127.3, 126.9, 126.4, 111.7, 60.1, 55.8, 53.5, 43.0, 37.4, 29.1; IR (KBr, $cm^{-1}$) 3324.5, 2928.1, 2835.5, 2316.6, 1593.3, 1451.5, 1423.5, 1251.9, 1248.0, 1034.8, 754.2; GC/MS (*m/z*, %): 281 (49.3), 280 (100.0), 264 (17.7), 250 (22.2), 236 (18.0), 221 (16.2), 165 (16.0). Characterization data are in accordance with the literature.[17b]

*(R)-Nornuciferine (**12b**)*[17]

To a microwave tube (10 mL) were added diastereoisomer **2b** (12.8 mg, 0.024 mmol), ethanol/water (2:1) (6 mL), and lithium hydroxide (10.1 mg, 0.24 mmol). The tube was sealed using a cap and the mixture was stirred under microwave heating at 180 °C (50 W) for 60 minutes. Then, the reaction was cooled to room temperature and distilled water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 15 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was

evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent, affording (*R*)-nornuciferine (**12b**). Yield: 4.6 mg (68%); yellowish oil; $R_f$ = 0.26 (eluent: methanol); $[\alpha]_D^{25}$ = -131.4º (*c* = 0.19 EtOH) ($[\alpha]_D^{22}$ lit[14c] = -105.2º (*c* = 1 EtOH)). $^1$H NMR and LRMS data obtained for compound **12b** were similar to those obtained for (*S*)-nornuciferine (**12a**).

*(S)-nuciferine (**1a**)*[17]

To a round-bottomed flask were added (*S*)-nornuciferine (**12a**) (19.0 mg, 0.068 mmol), methanol (11 mL), and a 37% (w/v) aqueous solution of formaldehyde (0.2 mL, 6.8 mmol). The mixture was maintained under magnetic stirring at room temperature for 30 minutes. Then, $NaBH_4$ (77 mg, 2.04 mmol) was added and the reaction was maintained under magnetic stirring at room temperature for 1 hour. Afterwards, brine (30 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 35 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent, affording (*S*)-nuciferine (**1a**). Yield: 18.2 mg (91%); yellowish solid; m.p. 163-165 °C (m.p. lit.[34] 163-165 °C); $R_f$ = 0.5 (eluent: methanol); $[\alpha]_D^{22}$ = +125.4º (*c* = 1 EtOH), $[\alpha]_D^{22}$ = +87.9º (*c* = 0.1 EtOH) ($[\alpha]_D^{21}$ lit[21] = +165º (*c* = 0.26 EtOH), $[\alpha]_D^{22}$ lit[14c] for (*R*)-nuciferine = -125.4º (*c* = 1 EtOH)); $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ 8.30 (d, *J* = 7.8 Hz, 1H), 7.25-7.16 (m, 3H), 6.56 (s, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 3.18-3.08 (m, 1H), 3.06-2.98 (m, 3H), 2.65-2.42 (m, 3H), 2.50 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ 151.9, 144.9, 136.1, 131.9, 128.4, 128.2, 127.8, 127.3, 127.2, 127.0, 126.7, 110.9, 62.1, 60.2, 55.7, 53.1, 43.7, 34.7, 28.8; IR (KBr, $cm^{-1}$) 2950.1, 2930.8, 2834.4, 1594.2, 1451.4, 1321.2, 1301.0, 1249.9, 1035.8; GC/MS (*m/z*, %): 295 (32.0), 293 (100.0), 278 (45.6), 264 (16.9), 250 (18.3), 235 (34.9). Characterization data are in accordance with the literature.[17b]

*(R)-nuciferine (**1b**)*[17]

To a round-bottomed flask were added (*R*)-nornuciferine (12b) (4.5 mg, 0.016 mmol), methanol (6 mL), and a 37% (w/v) aqueous solution of formaldehyde (0.05 mL, 1.6 mmol). The mixture was maintained under magnetic stirring at room temperature for 30 minutes. Then, $NaBH_4$ (18 mg, 0.48 mmol) was added and the reaction was maintained under magnetic stirring at room temperature for 1 hour. Afterwards, brine

(10 mL) was added to the mixture, which was extracted with ethyl acetate (3 x 15 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel using methanol as eluent, affording (*R*)-nuciferine (1b). Yield: 3.9 mg (84%); yellowish solid; m.p. 168-169 °C (m.p. lit.[35] 168 °C); $R_f$ = 0.5 (eluent: metanol); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -87.9º (*c* = 0.1 EtOH) ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ lit[14c] = -125.4º (*c* = 1 EtOH)); $^1$H NMR and LRMS data obtained for compound 1b were similar to those obtained for (*S*)-nuciferine (1a).

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## 6. Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/.

## 7. References

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Highlights

- Total syntheses of (*S*)- and (*R*)-nuciferine were accomplished through unprecedented approach involving benzyne chemistry.
- Reaction between chiral dihydroisoquinoline enamide and benzyne precursor afforded a separable mixture of diastereoisomers.
- The stereochemical pathway for the key transformation was evaluated by DFT calculations.
- The structure of the major diastereoisomer was unequivocally confirmed by X-ray analysis.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: